DOCKET NO. 17224 CON(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In Re Application of<br>John Sefton | Group Art Unit: 1617 |
| Serial No: 10/820,298 | Confirmation No: 7456 |
| Filed: April 7, 2004 | Examiner: Badio, Barbara P |
| For: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS | |

Honorable Commissioner of Patents and Trademarks
Alexandria, Virginia 22313-1450

**BRIEF ON APPEAL**

Dear Sir:

This appeal is taken from the final rejection of all of the claims in an Examiner's action mailed May 20, 2005. Oral hearing is waived.

## (1) REAL PARTY IN INTEREST

This patent application is assigned to Allergan, Inc, having its principal place of business at 2525 Dupont Drive, Irvine, CA 92612.

The parent case to this application, and any continuation, divisional, renewal, substitute, or reissue were originally assigned to Allergan Sales, Inc. via an assignment document recorded at Reel/Frame 011144/0193 on August 22, 2000.

Allergan Sales, Inc. (merged into Allergan Sales LLC 6/3/2002) assigned the parent case to this application, and any continuation, divisional, renewal, substitute, or reissue to Allergan, Inc. via an assignment document recorded at Reel/Frame 013898/0170 on April 7, 2003.

## (2) RELATED APPEALS AND INTERFERENCES

A. Notice of Appeal was filed in the parent case 09/367,712 on October 20, 2000. A new ground of rejection was issued in the Decision on Appeal by the Board on September 24, 2003.

B. A second Notice of Appeal was filed in the parent case 09/367,712 on March 9, 2004 (Appeal No. 2005-0938), which was decided in favor of Applicant on May 20, 2005.

## (3) STATUS OF CLAIMS

| Claims | Status |
|---|---|
| 1-11 | Rejected under 35 USC § 103 as being obvious |

## (4) STATUS OF AMENDMENTS

A response after final rejection was filed and considered, but not found persuasive by Examiner.

## (5) SUMMARY OF THE CLAIMED SUBJECT MATTER

Claim 1 provides a method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid. (Spec. p. 3, lines 8-10; p. 4, lines 16-20).

Claim 7 provides a method for treating psoriasis in a human subject by topically applying to the psoriatic skin of said subject an effective amount of tazarotene and an effective amount of a corticosteroid. (Spec. p. 3, lines 8-10).

## (6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

### Obviousness

A. The rejection of all claims under 35 U.S.C § 103(a) over Yamamoto (US 5,236,906) and Nagpal (US 5,650,279) in combination is the first ground of rejection to be reviewed on appeal.

B. The rejection of all claims under 35 U.S.C. § 103(a) as being unpatentable over Smith (US 5,874,074) or Sequiera (US 4,775,529) and Nagpal (5,650,279) in combination is the second ground of rejection to be reviewed on appeal.

## (7) ARGUMENT

## OBVIOUSNESS

### A. Rejection over Yamamoto and Nagpal

The claims are rejected as being obvious under 35 U.S.C. § 103 over Yamamoto (US 5,236,906) and Nagpal (US 5,650,279) in combination. In response to this, Applicant has provided evidence of unexpected results. If the Applicant correctly understand the Office Action's position, it disputes all of the Applicant's premises for asserting unexpected results except for one. These premises are listed below.

1) A general reduction of adverse events for the combination of tazarotene and a corticosteroid as compared to tazarotene alone is unexpected.
2) Combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone.
3) A general trend toward reduction in adverse events as corticosteroid potency is increased is unexpected.
4) There is a general trend toward reduction in adverse events as corticosteroid potency is increased.

Point 1 is an assertion of what a person of ordinary skill in the art would find unexpected. Point 2 is an assertion that Applicant's result was what a person of ordinary skill in the art would find unexpected according to point 1. Points 3 and 4 have a similar relationship. Point 3 does not appear to be disputed by the Office.

**1. A general reduction of adverse events for the combination of tazarotene and a corticosteroid as compared to tazarotene alone is unexpected.**

As a general principle, when a treatment with a therapeutically active agent is unchanged except that an additional therapeutically active agent is administered, an increase in side effects is expected. This assertion is supported by the affidavit, which says "[i]t is generally expected that administering two drugs to a patient will increase the adverse effects as compared to administering either of the individual drugs to the patient, where the dose of the individual drug is the same for individual and combination therapy." This is not attorney argument, but the testimony of an expert. The Office Action contradicted the expert and asserted "[t]he general expectation with combination therapy is a reduction in adverse effect." The Office Action claims that "[t]he adverse effect of the active ingredients might be different," and thus a person of ordinary skill in the art "would not expect" an increase in adverse events for a combination.

Applicants agree that active agents might have different side effects. However, a combination of those two active agents would still be expected to have an increase in adverse events. Generally, adverse events are additive. For example, if active agent A has adverse effects M and N, and active agent B has adverse effects Y and Z, one would expect that combining them without changing the dose of either A or B would result in adverse effects M, N, Y, and Z. Thus, the combination has more adverse events (4) than the individual active agents (2 each). Because the adverse event contribution of each of the drugs in a combination may be different, the total number of adverse events is the most important quantity to be evaluated in terms of unexpected results. Furthermore, many adverse effects are common among many drugs, so common adverse effects may be expected to increase when combining drugs. The Office Action has provided no evidence that a person skilled in the art at the time the application was filed would have believed

that the present combination would not have more adverse events than the individual components alone. By contrast, Applicant has provided expert testimony that the general rule in the art is that combining drugs ordinarily increases the adverse effects. Therefore, the evidence of record supports Applicant's assertion.

**2. Combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone.**

This assertion is also supported by the affidavit, which states "there appears to be a general trend that combinations of tazarotene and corticosteroids increase efficacy in the treatment of psoriasis while reducing the adverse events as compared to tazarotene alone." Again, the Office Action rejects the testimony of an expert, not attorney argument. The reason that the Office Action provided for not agreeing with this assertion is reproduced in its entirety below.

> Applicant also argues the data presented in Gollnick supports *the general trend of a reduction in adverse events with the combination of tazarotene and corticosteroids compared to tazarotene alone*. As stated in the previous Office Action, the *data shows no difference with the utilization of med- versus high-potency corticosteroid* and, thus, does not support the applicant's assertion of a trend towards a *decrease in adverse effect with increase in the potency of corticosteroid*. (Italics added.)

This reasoning does not even address the Applicant's assertion it was supposed to disprove. Note that the assertion of the Applicant in question is according to the Office Action that "the general trend of a reduction in adverse events with the combination of tazarotene and corticosteroids compared to tazarotene alone." However, the Office Action goes on to claim that the "data shows no difference with the utilization of med- versus high-potency corticosteroid." With all due respect, the comparison of medium to high potency corticosteroid is irrelevant to whether combining corticosteroids with tazarotene results in reduced side effects as compared to tazarotene alone. Thus, this does not disprove the Applicant's point. Finally, the conclusion drawn is not that adding a corticosteroid to tazarotene does not reduce adverse events, but that there is no "decrease in adverse effect with increase in potency of the corticosteroid." Thus, even if this conclusion could be drawn from that data (which the Applicant does not believe is the

case), it is unrelated to the actual question that was supposed to be addressed, and the Office Action has failed to prove its point.

Not only has the Office Action failed to prove its point, but if one were to take the conclusion that there is no "decrease in adverse effect with increase in potency of the corticosteroid" as true, the Applicant's assertion is even easier to prove. If there is no trend toward a decrease in adverse events with increasing corticosteroid potency, then all of the corticosteroids have essentially the same effect regardless of potency. If all of the corticosteroids have the same effect regardless of potency, then all of the corticosteroids can be treated the same when comparing them to tazarotene alone to determine whether the combination has reduced adverse events. Averaging the adverse event profile of the corticosteroid combination groups yields the data shown below. The table shows that corticosteroids significantly reduce the erythema significantly, and the pruritus and irritation somewhat. More importantly, as explained above, the total number of adverse events is the most relevant to unexpected reduction of side effects, and the table shows an undeniable reduction in the total number of adverse events for the combination treatment. Thus, if one accepts that there is no trend in reduction of adverse events with increasing corticosteroid potency, one is compelled to conclude that the combination reduces the total number of adverse events as compared to tazarotene alone.

| | Pruritus | Erythema | Irritation | Burning | **Total** |
|---|---|---|---|---|---|
| No steroid | 15 | 12 | 8 | 6 | **41** |
| Steroid | 14 | 6 | 6 | 5 | **32** |

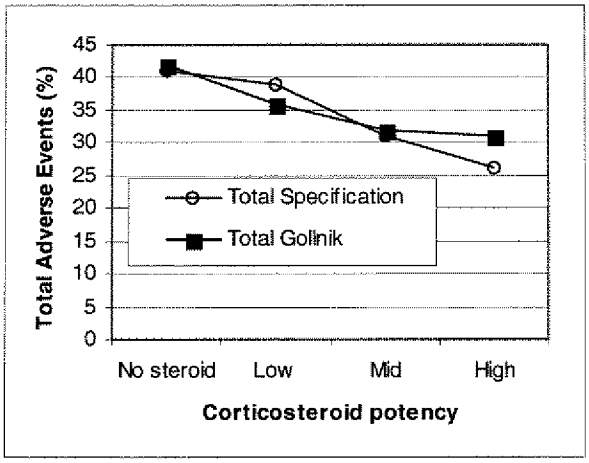
In conclusion, Applicant has presented an expert affidavit to support the assertion that combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone. The Office Action disagrees with this but provides evidence and reasoning that does not even address the assertion of Applicant that it was supposed to disprove. Finally, even if the conclusion drawn in the Office Action were true (which Applicant does not believe), then this conclusion would further strengthen, not weaken, Applicant's position.

**1. A general trend toward reduction in adverse events as corticosteroid potency is increased is unexpected.**

This assertion is supported by affidavit, which says "[i]t is generally expected that increasing the potency of a corticosteroid will increase the adverse events." Since this is not challenged by the Office Action, Applicants assume that this statement is accepted as true.

**2. There is a general trend toward reduction in adverse events as corticosteroid potency is increased.**

| | Total Adverse Events (%) Specification | Total Adverse Events (%) Gollnik |
|---|---|---|
| No steroid | 41 | 42 |
| Low | 39 | 36 |
| Mid | 31 | 32 |
| High | 26 | 31 |




The table and plot above show both the data from the specification and the Gollnick reference. One does not need to be an expert to discern a trend. However, an expert has stated in the aforementioned affidavit that "there appears to be a trend of reduction in adverse events for the combination treatment of tazarotene and corticosteroid as the potency of the corticosteroid is increased." Further, Gollnick also states "there was a trend towards a lower incidence of treatment-related adverse events as corticosteroid

potency increased." (p. 18, abstract, fifth line from bottom) Thus, two experts have observed the trend asserted by Applicants.

Once again, the Office Action disputes the experts, claiming that the data shows "no difference" between the adverse events of the mid- versus high potency corticosteroid. First, it is not even true that there is "no difference" between mid- and high potency corticosteroids. Although the difference between the mid- and high potency is not as great as some of the other comparisons, there is still a difference, particularly when viewed with the other data. It is not correct to draw a sweeping conclusion from the one pair of points which shows the least difference while ignoring the overwhelming weight of the data. As mentioned before, the total adverse events is the most important comparison for unexpected results in the present case, and the data clearly supports a trend of decreasing total adverse events with increasing corticosteroid potency.

The Office Action also claims that the data shows increase in burning in the taz/high group versus the other groups including the taz/plac group. It also shows an increase or no change in irritation in the taz/low versus the taz/plac group, similar incidence of erythema in all three groups given the corticosteroid; and an increase incidence of pruritus in taz/low group versus taz/plac group and an increase or no change in the taz/med group versus taz/plac.

Applicant points out that the fact that some data points are not consistent with a trend does not mean the trend does not exist. In fact, most real data contains outliers. The Office Action focuses on a few data points and ignores the overall picture. This is not a proper analysis of experimental data. Applicant again points to the table and plot of the total adverse events presented above. Surely the presence of a few outliers does not overcome the undeniable trend which is plainly discernable, and has been explicitly recognized by two experts in the affidavit and the Gollnik reference.

Since the original drafting of this brief on appeal, the Federal Circuit decided *Ferring BV v. Barr Laboratories*, holding that a patent applicant's failure to disclose his employer's past professional relationships with a group of scientists who submitted declarations to the PTO in support of the patentability of the claims constituted inequitable conduct. 437 F.3d 1181 (Fed. Cir, 2006). In light of this decision, Applicant

points out that the Gollnik authors have conducted clinical trials for Applicant's employee, and have acted as paid consultants for Applicant's employee.

Applicant has presented four assertions which, if true, demonstrate that the claimed combinations have unexpected results. The Office Action has disputed three of these assertions. Each of these assertions has been supported by an expert affidavit, and the Office has disputed these assertions without providing any support which stands up to reasonable scrutiny. Therefore, Applicants have demonstrated unexpected results for the claimed combinations.

**Concentration of the Corticosteroid**

This and the previous Office Actions continue to assert that the appropriate comparison is the concentration of the corticosteroid compound in the composition, and not the potency.

> ...like the data presented in the present specification, the comparison [in the Gollnik reference] is with different doses of corticosteroids. Based upon the utilization of the low, of low, med-, and high-potency, the skilled artisan would have the reasonable expectation that the effective amount of each group would decrease accordingly and thus, comparison would be based on decreasing doses of corticosteroid with increase potency. However, it is noted that the amount of high potency corticosteroid is twice the amount of med-potency corticosteroid in the present specification or for times the amount of low-potency corticosteroid in Gollnick reference.

As Applicant pointed out in previous responses, the appropriate comparison made by those skilled in the art is the potency of a corticosteroid formulation, not the concentration of the corticosteroid compounds. The reason the specification and the Gollnik reference compare results by potency is because that is the meter used in the art used to rank the efficacy and side effect profile of corticosteroid formulations. This method has been sanctioned by Applicant, Gollnik, and presumably the peer reviewers of the *British Journal of Dermatology*, the journal that published the Gollnik article. The Office Action has provided no evidence other than the unsupported opinion of the Examiner, that this is not a proper method. In the DECISION ON APPEAL of parent case Application No.

09/367,712, the Board also sanctioned Applicant's position on this issue. The relevant parts of that decision are reproduced below.

> **As we understand the examiner's assertion (Answer, p. 5), the evidence of record does not provide a "true side-by-side comparison" of the reagents because different concentrations of corticosteroids were used.** More specifically, in the Final Office Action, the examiner points out (bridging paragraph, pages 2-3), "Example 1 and the Figures compare alternative topical application of 0.1% tazarotene gel and a placebo, 1% hydrocortisone acetate (low-potency corticosteroid), 0.05% alcometasone dipropionate (medium-potency corticosteroid) or 0.1% betamethasone valerate (high-potency corticosteroid)." According to the examiner (Final Office Action, page 3), "in order to argue unexpected and/or unobvious results, the amount of corticosteroid in each case has to be kept constant.
>
> However, as appellant points out (Brief, page 5), since the potencies of the corticosteroids differ, a "comparison of a concentration of one compound to a concentration of a different compound is not proper." Rather, as we understand appellant's argument (Brief, page 6), the use of different concentrations of each corticosteroid effectively "normalizes" the corticosteroids relative to their potency. According to appellant (id.),
>
> > The potency of the corticosteroid is assigned according to the particular formulation in which it is contained. Thus, the 1% hydrocortisone acetate formulation used in the patent specification is considered to be low-potency at a concentration of 1% in the vehicle it is administered. The same is true for 0.05% alcometasone dipropionate being a medium-potency corticosteroid and 0.1% betamethasone valerate being a high-potency corticosteroid.
>
> According to appellant (id.), "[t]he whole point of assigning potency to a corticosteroid formulation is to indicate the activity of that formulation, and thus treatment for a particular condition is determined according to the assigned potencies of the various corticosteroid formulations." In support of this assertion appellant relies on Cornell (et. al. "Correlation of the Vasoconstriction Assay and Clinical Activity in Psoriasis," Arch Dermatol, Vol. 121, pp. 63-67). The examiner, however, fails to address appellant's argument or the Cornell reference, maintaining instead (Answer, page 5),
>
> > [t]he examiner sees no reason why applicant could not utilize similar amounts of corticosteroids in each case. In addition, the utilization of low-, mid- and high-potency would imply that at identical concentrations, the efficacy of corticosteroids would be as recited and, thus, the skilled artisan would expect the high-potency corticosteroid to be most effective when used at similar concentration as the others.

The examiner, however, appears to miss the point. As the examiner recognizes the concentration of high-potency corticosteroid used in the experiments was 10-fold less than the concentration of low-potency corticosteroid. As appellant points out (Brief, page 6), the

> [e]xaminer's position is inconsistent with itself in that [e]xaminer alleges "[t]he skilled artisan would have the reasonable expectation that the higher concentration of betamethasone valerate [(a high-potency corticosteroid)] would result in better improvement over treatment with lower concentrations of alcometasone dipropionate [a medium-potency corticosteroid)]" but fails to recognize that the same reasoning would lead a skilled artisan to expect that the lower concentrations of alcometasone dipropionate [(a medium potency corticosteroid)] and betamethasone valerate [(a high-potency corticosteroid)] relative to hydrocortisone acetate [(a low-potency corticosteroid)] would result in the treatment by the former two compounds being less effective. If the former two treatments are expected to be less effective, then the significant improvement of betamethasone valerate [(a high-potency corticosteroid)] over hydrocortisone acetate [(a low-potency corticosteroid)] that was observed must be unexpected.

Accordingly, **we are not persuaded by the examiner's unsupported assertion regarding appellant's evidence.** (footnotes omitted, full Cornell cite added, emphasis added)

Since the Board has already endorsed the Applicant's position on the issue of concentration. Applicant submits that the rejection on this ground is not proper.

**B. Smith or Sequiera and Nagpal**

The arguments made for part A "Rejection over Yamamoto and Nagpal" above also apply here.

In summary, the Office Actions have failed to provide any reasonable ground for rejecting Applicant's showing of unexpected results, and removal of the obviousness rejection is proper.

In view of the above, the Board is asked to reverse the Examiner's holding of all of the pending claims as unpatentable and direct the Examiner to pass the claims to issue.

Respectfully submitted,

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## (8) CLAIMS APPENDIX

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid.

2. The method of claim 1 wherein said corticosteroid is selected from the group consisting of fluocinolone acetonide, mometasone furoate, fluocinonide, diflorasone diacetate, fluticasone propionate, betamethasone dipropionate, clobetasol propionate, and betamethasone valerate.

3. The method of claim 1 wherein tazarotene is applied as a 0.1% gel.

4. The method of claim 1 wherein said corticosteroid is ~~a~~-selected from the group consisting of mometasone furoate, fluocinonide, alclometasone dipropionate, and betamethasone valerate.

5. The method of claim 4 wherein said corticosteroid is selected from the group consisting of alclometasone dipropionate, and betamethasone valerate.

6. A method for treating psoriasis in a human subject by topically applying to the psoriatic skin of said subject an effective amount of tazarotene and an effective amount of a corticosteroid.

7. The method of claim 6 wherein tazarotene is applied as a 0.1% gel.

8. The method of claim 7 wherein said corticosteroid is a cream.

9. The method of claim 8 wherein said corticosteroid is selected from the group consisting of mometasone furoate, fluocinonide, alclometasone dipropionate, and betamethasone valerate.

10. The method of claim 9 wherein said corticosteroid is selected from the group consisting of alclometasone dipropionate, and betamethasone valerate.

11. The method of claim 6 wherein tazarotene is administered once daily in the evening and the corticosteroid is administered once daily in the morning.

## (9) EVIDENCE APPENDIX

The following evidence is included appended herewith.

1. A 37 C.F.R. § 1.132 declaration entered into the record on February 8, 2005.
2. The Gollnik reference: H. Gollnik and A. Menter, *British Journal of Dermatology* 1999; **140** (Supp. 54): 18-23, entered into the record on April 7, 2004.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
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| Serial No: 10/820,298 | Confirmation No: 7456 |
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| For: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS | |

**DECLARATION OF AN EXPERT REGARDING FACTS RELEVANT TO PATENTABILITY (37 C.F.R. § 1.132)**

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

**PURPOSE OF DECLARATION**

1. This declaration is to establish evidence of patentability of one or more claims of the above referenced application.

2. The person making this declaration is an expert in the relevant art.

**TESTIMONY OF EXPERT RELEVANT TO PATENTABILITY**

3. Based upon the evidence in United States Patent Application Serial Number 10/820,298 and in H. Gollnick and A. Menter *British Journal of Dermatology* 1999; 140 (Suppl. 54): 18-23, there appears to be a general trend that combinations of tazarotene and corticosteroids increase efficacy in the treatment of psoriasis while reducing the adverse events as compared to tazarotene alone.

4. It is generally unexpected that a treatment would increase efficacy while reducing adverse events.

5. It is generally expected that administering two drugs to a patient will increase the adverse effects as compared to administering either of the individual drugs to the patient, where the dose of the individual drug is the same for individual and combination therapy.

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.10
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE WITH SUFFICIENT POSTAGE AS EXPRESS MAIL (LABEL NO. EV295681885US IN AN ENVELOPE ADDRESSED TO: COMMISSIONER FOR PATENTS, ALEXANDRIA, VA 22313-1450 ON FEBRUARY 8, 2005.
Printed name of person making deposit: Susan Bartholomew
Signature: Susan Bartholomew Date: FEBRUARY 8, 2005

6. Further, based upon the same evidence, there appears to be a trend of reduction in adverse events for the combination treatment of tazarotene and corticosteroid as the potency of the corticosteroid is increased.

7. It is generally expected that increasing the potency of a corticosteroid will increase the adverse events.

8. Finally, based upon said evidence, increased efficacy and reduced adverse events relative to 0.1% tazarotene gel treatment alone for the following combinations is observed: 0.1% tazarotene gel plus 0.1% mometasone furoate; 0.1% tazarotene gel plus 0.05% fluocinonide; 0.1% tazarotene gel plus 0.05% alclometasone dipropionate; and 0.1% tazarotene gel plus 0.1% betamethasone valerate. This combination of increased efficacy and reduced adverse events is unexpected.

## TIME OF PRESENTATION OF THE DECLARATION

This declaration is submitted prior to final rejection.

## DECLARATION

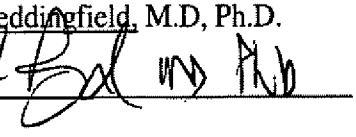
8. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on Information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

## SIGNATURE(S)

**7. Expert in the Medical Art**

Full name expert: Frederick Beddingfield, M.D, Ph.D.

Expert's signature:  Date: February 2, 2005

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*British Journal of Dermatology* 1999; 140 (Suppl. 54): 18–23.

# Combination therapy with tazarotene plus a topical corticosteroid for the treatment of plaque psoriasis

H.GOLLNICK AND A.MENTER*

*Chairman, Department of Dermatology & Venereology, Otto-von-Guericke-Universität, Magdeburg, Germany, and *Chairman, Division of Dermatology, Baylor University Medical Center, Dallas, Texas, U.S.A.*

**Summary** Although tazarotene monotherapy is generally efficacious and well tolerated, studies show that both the efficacy and the tolerability of tazarotene therapy can be further improved when it is used in combination with certain topical corticosteroids. The studies reported here evaluate the usefulness of two potential combination regimens. In one regimen, a corticosteroid is added to tazarotene treatment. In the other regimen, corticosteroid treatment alternates on a daily basis with tazarotene treatment. The results of the first study, which involved 300 patients, showed that additive combination therapy using tazarotene plus a mid- or high-potency topical corticosteroid significantly increased the percentage of plaques achieving treatment success at the end of the treatment period, compared with tazarotene plus placebo (91% and 95% vs. 80%, respectively; $P<0{\cdot}05$ for both). Similarly, tazarotene plus a mid- or high-potency topical corticosteroid reduced the incidence of patient withdrawals compared with tazarotene plus placebo (5·5% and 9·6% vs. 13·3%). The results of the second study, which involved 398 patients, showed that a combination regimen that alternates between tazarotene and a high-potency topical corticosteroid treatment each day, significantly increased the treatment success rate compared with regimens using tazarotene alternating with a mid-potency corticosteroid or placebo (75% vs. 55% and 54%, respectively, at the end of the treatment period; $P<0{\cdot}05$ for both). In addition, there was a trend towards a lower incidence of treatment-related adverse events as corticosteroid potency increased (from 42% with tazarotene plus placebo to 36%, 32%, and 31% with tazarotene plus the low-, mid-, and high-potency corticosteroid, respectively). Both treatment regimens are potentially useful and offer a rational approach to optimizing the efficacy and tolerability of tazarotene treatment for plaque psoriasis.

*Key words*: combination, corticosteroid, psoriasis, tazarotene, topical.

## Introduction

The main therapeutic options for the treatment of patients with stable plaque psoriasis include emollients, keratolytic agents, tar preparations, corticosteroids, topical or oral retinoids, vitamin D analogues, anthralin, and phototherapy. Each treatment has its relative advantages and disadvantages and, as in other areas of clinical medicine, various combinations of these treatments have been investigated in an attempt to improve the overall efficacy, tolerability, and acceptability of therapy.[1] Rotational therapy has also been used to maximize efficacy and minimize the risk of adverse events.[2–4] In such therapy, patients are switched between different monotherapies or combination therapies according to the stage and type of psoriasis and the patient's individual needs.

Topical treatments are the most widely used therapy in patients with mild-to-moderate psoriasis because only a limited area of their skin is affected and the use of systemic therapies, with their attendant problems, is not warranted. In the U.S.A., corticosteroids have tended to be the most widely used of the topical agents[5] because of their relatively good efficacy, tolerability, cosmetic acceptability, and cost. The prolonged use of topical steroids, however, can be associated with resistance and a rebound effect on withdrawal of treatment.[6] The early topical retinoids that were available before the approval of tazarotene were generally found to have only limited efficacy or to induce intolerable skin irritation.[7–10] Because tazarotene is selective for RAR-γ and RAR-β receptors, it has a more targeted action on psoriatic keratinocytes compared with older

Correspondence: Professor H.P.M.Gollnick, Department of Dermatology & Venereology, Otto-von-Guericke-Universität, Magdeburg, Germany.

retinoids and helps prevent stimulation of those retinoid pathways that are apparently unrelated to the pathophysiology of psoriasis. This is likely to promote both good efficacy and good tolerability.

Combination therapy with tazarotene and a topical corticosteroid appears logical because these agents have some different (as well as some common) mechanisms of action, and thus are likely to have additive or synergistic effects. Although the exact mechanism of action of tazarotene remains to be fully elucidated, it is known to induce the expression of at least three so-called 'tazarotene-induced genes' (TIGs).[11–13] Our understanding of the role of the proteins expressed by these genes is limited, but the product of TIG-1 is believed to function as a cellular adhesion molecule to promote better cell–cell contact and reduce keratinocyte proliferation,[11] and the product of TIG-2 may be a soluble ligand for cell surface receptors.[12] TIG-3 may be involved in tumour suppression.[13] Whatever the precise mechanism of action of tazarotene, studies suggest that it helps correct three of the major pathogenic features of psoriasis: keratinocyte hyperproliferation (Allergan Inc., data on file), abnormal keratinocyte differentiation,[14] and infiltration of inflammatory components.[14]

Corticosteroids also have anti-proliferative and anti-inflammatory properties and, in addition, have immunosuppressive effects.[15] In contrast to tazarotene, the mechanism of action of corticosteroids is thought to be mediated through the induction of phospholipase $A_2$ inhibitory proteins, which inhibit the synthesis of various cytokines.[16] The antigen-induced release of such cytokines is thought to contribute to the inflammation associated with psoriasis,[17] and such a mechanism of action would therefore explain the anti-inflammatory actions of corticosteroids.

Previous studies have shown the relative advantages of retinoids and corticosteroids. The addition of a non-receptor-selective topical retinoid to corticosteroid therapy has been shown to at least partially ameliorate corticosteroid-induced epidermal atrophy.[18,19] Similarly, treatment with tazarotene, the first receptor-selective topical retinoid, has been observed to reverse some of the skin atrophy induced by superpotent corticosteroid therapy (Dr Prystowsky, personal communication), and also to be associated with a lower cumulative probability of relapse 12 weeks post-treatment compared with corticosteroid therapy.[20] Advantages of corticosteroids include their ability to improve the efficacy of retinoic acid therapy[10] and to reduce the incidence of retinoic acid-induced skin irritation.[8]

It is timely to perform further investigations into potential therapeutic regimens utilizing both tazarotene and topical corticosteroids. The results of two large, multicentre studies that evaluated two such potential regimens are reported here. The first study evaluated the clinical benefits of adding a low-potency, mid-potency, or high-potency topical corticosteroid to tazarotene therapy. The second study utilized a combination regimen that switched between tazarotene therapy and topical corticosteroid therapy every day. Although rotational therapy using dithranol, $D_3$-derivatives, corticosteroids, and/or ultraviolet light as monotherapy or combination therapy is well known,[1–4,21,22] the concept of an alternate-day regimen of corticosteroids with other topical drugs remains relatively unexplored. It is somewhat surprising that such alternate-day regimens have not been more widely investigated.

## Subjects and methods

### *Additive combination of tazarotene plus corticosteroid*

A multicentre, investigator-masked, parallel-group study was performed in order to investigate the efficacy and tolerability of combination tazarotene and topical corticosteroid treatment.[23] All patients were at least 21 years of age and had stable plaque psoriasis on no more than 20% of their body surface area (BSA). Patients were randomized to receive tazarotene 0·1% gel once daily in the evening plus one of the following once daily in the morning: low-potency corticosteroid cream (0·01% fluocinolone acetonide), mid-potency corticosteroid cream (0·1% mometasone furoate), high-potency corticosteroid cream (0·05% fluocinonide), or placebo (vehicle) cream. The treatment period was 12 weeks in duration and patients were followed for an additional 4 weeks after treatment had ended.

Comparisons among the four treatment groups were performed by the two-way ANOVA model. If among-group differences were significant (overall $F$-test at $P \leq 0{\cdot}05$), between-group comparisons were performed by means of Fisher's protected least significant differences test.[24]

### *Alternating between tazarotene and corticosteroid each day*

A multicentre, double-blind, parallel-group study was performed to evaluate the efficacy, tolerability, and acceptability of alternate-day treatment with tazarotene gel and a corticosteroid cream. All patients were at least 21 years of age and had stable plaque psoriasis on no more than 20% of their BSA. Patients were randomized

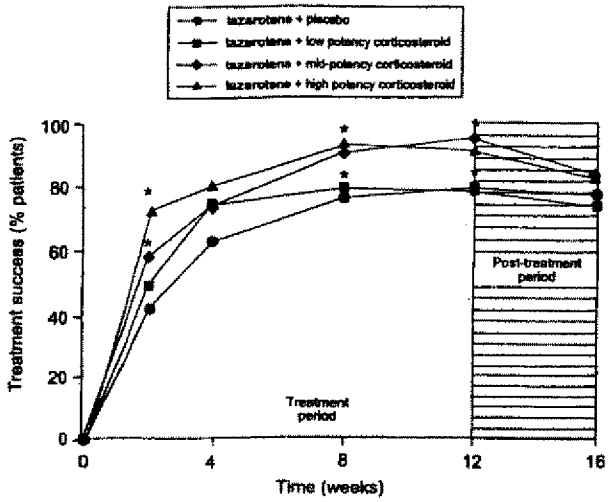



Figure 1. Percentage of patients achieving treatment success (≥ 50% global improvement in psoriasis) during treatment with tazarotene 0·1% gel plus placebo or a low-, mid-, or high-potency topical corticosteroid, both given once daily for 12 weeks.

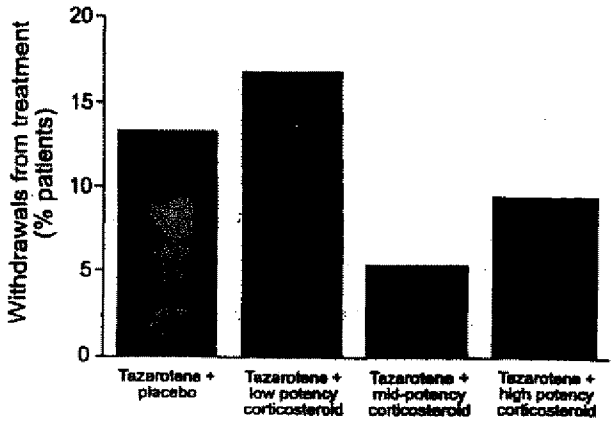



Figure 2. The incidence of patients withdrawing from treatment with tazarotene 0·1% gel plus placebo or a topical corticosteroid (low, medium or high potency), both given once daily for 12 weeks.

to receive tazarotene 0·1% gel every other evening for 12 weeks and, on the intervening evenings, to receive one of four creams: placebo, low-potency corticosteroid (1% hydrocortisone acetate), medium-potency corticosteroid (0·05% alclometasone dipropionate), or high-potency corticosteroid (0·1% betamethasone valerate; classified as a mid-potency steroid in the U.S.A.). The 12-week treatment period was followed by a 4-week follow-up period.

Primary efficacy variables were the global response to treatment and the degree of plaque elevation. A 7-point scale was used to assess the global response to treatment (completely cleared, almost cleared, marked response, moderate response, slight response, condition unchanged, condition worsened). Treatment success was again defined as ≥ 50% global clinical improvement in psoriasis.

Secondary efficacy variables included the degree of scaling and the degree of erythema. A 9-point grading scale was used to assess the degree of plaque elevation, scaling, and erythema (grade 0 = none; 2 = mild; 4 = moderate; 6 = severe; and 8 = very severe, with 1, 3, 5, and 7 serving as mid-points). A 2-point reduction on this scale was considered clinically significant. Superiority was defined as a statistically significant difference between treatments ($P \leq 0{\cdot}05$).

Baseline and changes from baseline at each subsequent visit were analysed using the extended Cochran–Mantel–Haenszel test for ordinal data stratified by country[25] employing modified ridit scores.[26,27] Within-group comparisons to baseline at each follow-up visit were performed by the Wilcoxon signed-rank test. Pair-wise between-group comparisons were considered significant only if the overall Cochran–Mantel–Haenszel test was significant.

## Results

*Additive combination of tazarotene plus corticosteroid*

A total of 300 patients were enrolled from centres across the USA and Canada.

*Treatment success.* Treatment success was defined as ≥ 50% global improvement in the appearance of the lesions. Treatment success rates were consistently higher in patients treated with tazarotene plus the mid- or high-potency corticosteroid (taz/mid and taz/high, respectively), compared with those treated with tazarotene plus placebo or the low-potency corticosteroid (taz/plac and taz/low, respectively) (Fig. 1). Treatment success rates with taz/mid and taz/high were significantly higher than taz/plac at Weeks 2, 8, and 12 of treatment. At Week 12, treatment success rates were 91% with taz/mid and 95% with taz/high, compared with 80% with taz/plac ($P < 0{\cdot}05$ for both). Plaques treated with taz/mid or taz/high also reached initial treatment success significantly faster than plaques treated with taz/plac (a median time of 2 and 3 weeks, respectively, compared with 4 weeks).

*Plaque elevation, scaling, and erythema.* All treatment groups experienced significant reductions in plaque elevation, scaling, and erythema from baseline

values. There were no significant between-group differences in the degree of plaque elevation, but the degree of scaling was consistently and significantly lower in the plaques treated with taz/mid or taz/high than in the taz/plac group throughout the treatment period. At Week 4, erythema was significantly lower in the groups receiving tazarotene plus the higher potency corticosteroids than in both of the other groups.

*Adverse events.* Local skin reactions (burning, pruritus, and erythema), typically associated with topical retinoid therapy, were the most common adverse events that occurred in the study. There was a trend towards a lower incidence of treatment-related adverse events in patients receiving mid- and high-potency corticosteroids compared with those receiving the placebo or low-potency corticosteroid (for example, 4·2% and 11·4% of patients experienced burning vs. 14·5% and 18·1% after 2 weeks, respectively). There was also a lower incidence of patient withdrawals in the groups receiving mid-potency (5·5%) or high-potency corticosteroids (9·6%), compared with the groups receiving placebo (13·3%) or low-potency corticosteroid (16·7%) (Fig. 2). As patient withdrawal rates can be an indication of the severity of adverse events, they are perhaps a truer reflection of the clinical importance of adverse events than the incidence rates of adverse events alone are.

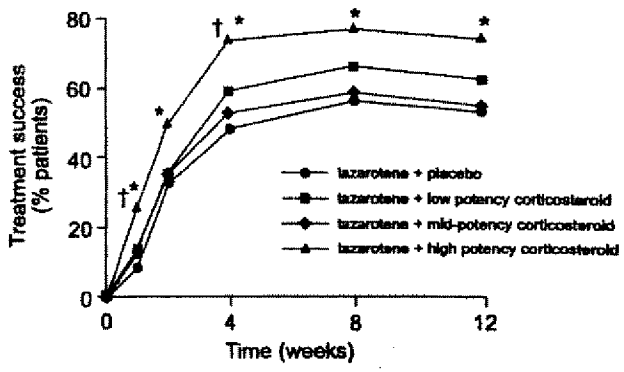
*Alternating between tazarotene and corticosteroid each day*

A total of 398 patients, of which 388 were evaluable for efficacy, were enrolled in the study from 41 centres across France, Germany, and The Netherlands.

*Treatment success.* Although all treatment groups achieved treatment success rates of >50% within 8 weeks, the most efficacious treatment was clearly the taz/high combination (Fig. 3). This treatment achieved significantly greater treatment success rates than the taz/plac and taz/mid combinations throughout the 12-week treatment period ($P<0·05$). The taz/high combination also achieved significantly greater treatment success rates than the taz/low combination at weeks 1 and 4 ($P<0·05$).

In addition, the taz/high combination achieved initial treatment success significantly faster than any of the other combinations. The median time to initial treatment success was 2 weeks in the taz/high group, compared with 4 weeks in each of the other groups.

Of the 368 patients who completed 12 weeks' treatment, 210 (57·1%) patients returned for the post-treatment visit. In this subgroup of patients, the treatment success rate was ≥ 60% in each treatment group. There were no significant between-group differences.




* $P < 0.05$ vs tazarotene + placebo and tazarotene + mid-potency corticostroid;
† $P < 0.05$ vs tazarotene + low potency corticosteroid

Figure 3. Percentage of patients achieving treatment success (≥ 50% global improvement in psoriasis) when treated for 12 weeks with tazarotene 0·1% gel every other day plus placebo or a low-, mid-, or high-potency topical corticosteroid on the intervening days.

*Plaque elevation.* All treatment groups achieved statistically significant reductions in plaque elevation from baseline during the study, with the taz/high group achieving consistently greater reductions than the other treatments throughout the treatment period. At week 4, these reductions were significantly greater than those in all the other treatment groups ($P<0·05$). The taz/high combination also achieved clinically significant reductions in plaque elevation more rapidly than the other treatments—in 2 weeks, compared with 4 weeks in all the other groups. Generally, the reductions in plaque elevation achieved by week 12 did not vary markedly during the ensuing 4-week follow-up period.

*Scaling.* As with the results for plaque elevation, all treatment groups achieved statistically significant reductions in scaling from baseline during the treatment period. At week 4, the reductions in scaling were significantly greater in the plaques treated with taz/high than in the plaques treated with taz/plac or taz/mid ($P<0·05$). The reductions in scaling achieved in all groups by the end of the treatment period remained largely unchanged during the 4-week follow-up period.

*Erythema.* All treatment groups achieved statistically significant reductions in erythema from baseline during the treatment period (taz/plac from week 2 onwards).

The tazarotene plus high-potency corticosteroid combination was the most efficacious treatment, achieving significantly greater reductions in erythema than any of the other treatments at weeks 4 and 8 ($P<0·05$), and clinically significant improvements in erythema at weeks 8 and 12.

During the follow-up period there were no significant between-group differences. All groups retained statistically significant reductions in erythema compared with baseline levels.

*Adverse events.* The majority of adverse events in all four treatment groups were mild to moderate in severity, and consisted predominantly of local irritation, including pruritus, erythema, and burning skin. The incidence of treatment-related adverse events decreased with increased corticosteroid potency, falling from 42% in the taz/plac group, to 36%, 32%, and then 31% in the taz/low, taz/mid, and taz/high groups, respectively. There were no statistically significant differences in the incidence of adverse events between treatment groups, and no clinically meaningful increases in the incidence of treatment-related adverse events over the 12-week treatment period. The incidence of discontinuations due to adverse events was 14–16% in all groups, with no apparent between-group differences.

Twelve patients experienced serious adverse events (taz/plac, three patients; taz/low, one; taz/mid, five; taz/high, three), but all such events were judged unrelated to the study treatment.

## Discussion

Tazarotene has previously been shown to offer improved tolerability compared with non-selective retinoids. Both studies reported here demonstrate that utilizing a topical corticosteroid cream in combination with tazarotene can further improve both efficacy and tolerability compared with tazarotene plus placebo cream. The two therapies complement one another. The corticosteroid enhances efficacy and ameliorates the perilesional irritation that may arise with topical retinoids such as tazarotene. Furthermore, the efficacy of tazarotene allows the dose of corticosteroid to be minimized, thus lowering the potential for corticosteroid-induced adverse events such as epidermal atrophy.

In the studies reported here, the benefits of using a mid- or high-potency corticosteroid in an *additive* combination regimen with tazarotene, compared with tazarotene plus placebo, included significant improvements in several measures of efficacy—higher rates of treatment success, faster achievement of initial treatment success, a lower degree of scaling, and a transiently lower degree of erythema. The benefits of using a high-potency corticosteroid in an *alternating* combination regimen with tazarotene included significantly higher rates of treatment success and significantly faster achievement of initial treatment success. Whereas the benefits of the additive regimen were achievable with either the mid-potency or the high-potency corticosteroid, the benefits of the alternating regimen were predominantly associated with the use of the high-potency corticosteroid (betamethasone valerate). However, as the potency ranking of corticosteroids differs between countries (betamethasone valerate 0·1% is classified as a high-potency steroid in Europe and a mid-potency steroid in the U.S.A.), it is difficult to generalize about specific potency issues.

In both studies, one group of patients was treated with tazarotene plus vehicle cream (rather than tazarotene alone) in order to control any potential influence from the cream base of the steroids as well as to replicate good clinical practice. (In addition, we recommend the use of emollients in order to help maximize the efficacy and tolerability of tazarotene monotherapy.) In clinical practice, if patients are not using emollients, then the efficacy and tolerability benefits of adding a corticosteroid to tazarotene treatment are likely to be even more pronounced than indicated in these studies.

In countries that currently do not favour the use of topical corticosteroids to treat plaque psoriasis, the results of these studies are likely to lead to a revival in the use of corticosteroids and thus a change in the therapeutic armamentarium. It is logical to treat chronic plaque psoriasis with two agents that have additive or synergistic effects and further research is now required to determine the optimal dose regimen for combination therapy utilizing tazarotene and a corticosteroid. In clinical practice, in order to minimize the risk of steroid rebound and other steroid-induced adverse effects, it may be advisable to slowly wean patients off the steroid after the initial 3–4 weeks as the clinical effect from tazarotene starts to become apparent, and then to continue treatment with tazarotene monotherapy (non-atrophogenic mid-potency corticosteroids such as methyprednisone-aceponat or prednicarbet).

The addition of a mid- or high-potency topical corticosteroid to tazarotene therapy offers a valuable means of optimizing the efficacy and tolerability of treatment for plaque psoriasis. Both the additive and the alternating regimens reported here appear to

offer significant clinical advantages over tazarotene monotherapy.

## Acknowledgements

The cooperation of all investigators and patients in these studies is gratefully acknowledged.

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## (10) RELATED PROCEEDINGS APPENDIX

The following related decisions by the board are appended herewith.

1. A Decision on Appeal by the Board issued September 24, 2003 on application serial number 09/367,712.
2. A Decision on Appeal by the Board issued May 20, 2005 on application serial number 09/367,712.

Paper No. 15

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte JOHN SEFTON

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Appeal No. 2002-1369
Application 09/367,712

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ON BRIEF

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Before WILLIAM F. SMITH, ADAMS, and POTEATE, Administrative Patent Judges.

POTEATE, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's refusal to allow claims 1-3, 5-8 and 10-13, which are all of the claims pending in the application. Claim 1 is representative of the subject matter on appeal and is reproduced below:

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a mid-or high-potency corticosteroid.

The references relied upon by the examiner are:

| | | |
|---|---|---|
| Sequeira et al. (Sequeira) | 4,775,529 | Oct. 4, 1988 |
| Yamamoto | 5,236,906 | Aug. 17, 1993 |
| Nagpal et al. (Nagpal) | 5,650,279 | Jul. 22, 1997 |
| Smith | 5,874,074 | Feb. 23, 1999 |

GROUNDS OF REJECTION

1. Claims 1-3, 5-8 and 10-13 stand rejected under 35 U.S.C. § 103 as unpatentable over Yamamoto and Nagpal.

2. Claim 2 stands rejected under 35 U.S.C. § 103 as unpatentable over Smith or Sequeira in combination with Nagpal.

We affirm as to the first ground of rejection, but denominate our rejection as a new ground of rejection under 37 CFR § 1.196(b) for the reasons set forth below. Having concluded that the claims are unpatentable over Yamamoto and Nagpal, we do not reach the second ground of rejection.

DISCUSSION

The invention is directed to a method of treating proliferative skin diseases, e.g., psoriasis, in humans comprising administering an effective amount of tazarotene and an effective amount of a mid- or high-potency corticosteroid. In a preferred embodiment, the corticosteroid is selected from the group consisting of alclometasone dipropionate, momentasone furoate, and betamethasone valerate. Claim 2. According to

appellant, the combination of tazarotene and a mid- or high-potency corticosteroid provides a synergistic effect. Appeal Brief, Paper No. 11, received January 12, 2001, page 2.

The examiner found that Yamamoto teaches that it is known in the art to use adrenocortical hormones which are among those utilized by appellant for treatment of skin diseases including psoriasis. See Examiner's Answer, Paper No. 12, mailed March 8, 2001, page 3. The examiner further found that Nagpal discloses that it is known to use tazarotene for treatment of psoriosis. Id. The examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to have used the combination of mid- or high-potency corticosteroid and tazarotene for the treatment of proliferative skin diseases as claimed in view of the combined teachings of Yamamoto and Nagpal. See id., page 4. In so concluding, the examiner cites In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980) for the proposition that it is obvious to use the combination of two compounds/compositions taught by the prior art to be useful for the same purpose to form a third composition. Id.

Appellant is in agreement with the examiner's findings with respect to the teachings of the individual references. See Appeal Brief, page 4. However, appellant argues that the

examiner has not supplied the requisite motivation to combine the cited references to achieve the claimed invention. See id., page 5.

We disagree with appellant and conclude that the examiner has provided proper motivation for combining the references in accordance with the decision in Kerkhoven. Accordingly, we find that the examiner has established a prima facie case of obviousness.

A prima facie case of obviousness may be rebutted if the appellant shows that the art, in any material respect, teaches away from the claimed invention. In re Malagari, 499 F.2d 1297, 1303, 182 USPQ 549, 553 (CCPA 1974). Appellant argues that "Yamamoto '906 teaches away from the use of corticosteroids at the usual clinical doses in combination with active ingredients." Appeal Brief, page 5. In this regard, appellant notes that Yamamoto dilutes the "effective and usual concentration" of fluocinonide, i.e., .05%, to .015% or .005%. We do not find this argument persuasive since the Specification indicates that an effective amount of corticosteroid is in the preferred range of from about .005% to about .1% by weight of the composition. See Specification, page 5, lines 15-18.

A prima facie case of obviousness may be rebutted by

evidence showing that the claimed composition has "unexpected" properties which are not possessed by the prior art. In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). Appellant argues that the Specification provides evidence that mid- or high-potency corticosteroids in combination with tazarotene exhibit a synergistic effect, i.e., that the combination provides a more effective treatment of psoriasis than tazarotene alone, or in combination with a low-potency corticosteroid. Appeal Brief, pages 5-6. We have reviewed the evidence presented in the Specification and conclude that it is not persuasive in overcoming the examiner's prima facie showing of obviousness.

Referring, first, to Example 1, the results of which are set forth in Figure 1, we note that the combination of tazarotene and a low-potency corticosteroid appear to provide better results than the combination of tazarotene and a mid-potency corticosteroid in reducing the severity of psoriasis in patients treated over a period of 12 weeks. The mean severity was approximately the same for patients treated with these compositions after a further 4 week post-treatment. Moreover, it is impossible to conclude from Table II that the incidence of adverse events was consistently lower in patients treated with

mid- or high-potency corticosteroid in combination with tazarotene as compared with patients treated with low-potency corticosteroid in combination with tazarotene, or tazarotene alone. In particular, we note that patients suffered greater burning when treated with a combination of tazarotene and high-potency corticosteroid and a higher incidence of pruritus when treated with a combination of mid-potency corticosteroid and tazarotene.

Figure 2 shows treatment success in patients over a 12 week treatment period and four week post treatment period using the same four compositions. As with the results shown in Figure 1, it appears that the combination of low-potency corticosteroid and tazarotene provides better results than the combination of mid-potency corticosteroid and tazarotene.

We have also reviewed Example 2 of the Specification wherein appellant indicates that Example 1 was repeated using different corticosteriods in combination with tazarotene. See Specification, page 13. We do not find this Example persuasive in demonstrating unexpected results since the Example is unsupported by any data and is merely appellant's assertions that higher treatment success rates and decreased incidence of adverse events were provided when tazarotene was utilized in combination

with mid- or high-potency corticosteroids.

Accordingly, we conclude that appellant's evidence of unexpected results is insufficient to overcome the examiner's prima facie showing of obviousness. However, as the examiner failed to comment on appellant's evidence, we denominate our affirmance of the rejection as a new ground of rejection under 37 CFR § 1.196(b). See In re Wagner, 371 F.2d 877, 883, 152 USPQ 552, 558 (CCPA 1967) (proof of facts may be controverted by the Patent Office but cannot be ignored).

Having concluded that all of the claims are unpatentable under 35 U.S.C. § 103 in view of the combined teachings of Yamamoto and Nagpal[1], we do not reach the separate rejection of claim 2 under 35 U.S.C. § 103 as unpatentable over Smith or Sequeira in view of Nagpal.

---

[1]Appellant argues that claims 1-3, 5 and 12 are separately patentable from claims 6-8, 10, 11 and 13. Appeal Brief, page 3. However, appellant appears to present the same arguments with respect to both groups of claims in that he argues that the data provided in Examples 1 and 2 support the patentability of both groups of claims. See Appeal Brief, pages 6 and 7.

This decision contains a new ground of rejection pursuant to 37 CFR § 1.196(b)(amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

37 CFR § 1.196(b) also provides that appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

> (1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .
>
> (2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED; 37 CFR 1.196(b)

WILLIAM F. SMITH )
Administrative Patent Judge )
)
)
) BOARD OF PATENT
DONALD E. ADAMS ) APPEALS AND
Administrative Patent Judge ) INTERFERENCES
)
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# UNITED STATES PATENT AND TRADEMARK OFFICE

## BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOHN SEFTON



Appeal No. 2005-0938
Application No. 09/367,712

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and POTEATE, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-3, 5-8 and 10-13, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a high-potency corticosteroid.

The references relied upon by the examiner are:

| | | |
|---|---|---|
| Yamamoto | 5,236,906 | Aug. 17, 1993 |
| Nagpal et al. (Nagpal) | 5,650,279 | Jul. 22, 1997 |

## GROUND OF REJECTION

Claims 1-3, 5-8 and 10-13 stand rejected under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal.

We reverse.

## PROCEDURAL BACKGROUND

This is the second time this application is before us on appeal. On September 24, 2003, a Decision was entered in the first appeal (Appeal No. 2002-1369) affirming a rejection of claims 1-3, 5-8 and 10-13 under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal. Having concluded that the claims were upatentable over Yamamoto and Nagpal, the panel did not reach the only other ground of rejection in Appeal No. 2002-1369 - a rejection of claim 2 under 35 U.S.C. § 103 as being unpatentable over Smith[1] or Sequeira[2] in combination with Nagpal.[3] For clarity, we reproduce representative claim 1, as it was presented in 2002-1369, below:

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a mid- or high-potency corticosteroid.

As set forth in the Decision, page 3, "the examiner found Yamamoto teaches that it is known in the art to use adrenocortical hormones which are

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[1] Smith 5,874,074 Feb. 23, 1999

[2] Sequeira et al. (Sequeira) 4,775,529 Oct. 4, 1988

[3] A rejection of claim 2 under 35 U.S.C. § 103 as being unpatentable over Smith or Sequeira in combination with Nagpal was not presented to us on this appeal. Accordingly, we interpret this to mean that the examiner has withdrawn the rejection. Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys., 804 F.2d 659, 663, 231 USPQ 649, 651-652 (Fed. Cir. 1986), cert. denied, 480 U.S. 933 (1987).

among those utilized by appellant for treatment of skin diseases including psoriasis." In addition, the prior Merits Panel noted (id.), "[t]he examiner further found that Nagpal discloses that it is known to use tazarotene for treatment of psoriosis." According to the Decision (id.), the "examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to have used the combination of mid- or high-potency corticosteroid and tazarotene for the treatment of proliferative skin diseases as claimed in view of the combined teachings of Yamamoto and Nagpal." Based on this evidence, the prior Merits Panel found (Decision, page 4), "the examiner has provided proper motivation for combining the [Yamamoto and Nagpal] references in accordance with the decision in Kerkhoven[4]." Accordingly, the rejection of claims 1-3, 5-8 and 10-13 under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal, was affirmed.[5]

In affirming the rejection, the Merits Panel reviewed appellant's evidence of nonobviouness and made the following findings:

1. "Referring, first, to Example 1, the results of which are set forth in Figure 1, we note that the combination of tazarotene and a low-potency corticosteroid appear to provide better results than the combination of tazarotene and a mid-potency corticosteroid in reducing the severity of psoriasis in patients treated over a period of 12 weeks." Decision, page 5, emphasis added.

2. "[I]t is impossible to conclude from Table II[, appellant's specification, page 12,] that the incidence of adverse events was consistently lower

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[4] In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980).

[5] We note, however, the prior Merit Panel's statement (Decision, page 7), "as the examiner failed to comment on appellant's evidence, we denominate our affirmance of the rejection as a new ground of rejection...."

in patients treated with mid- or high-potency corticosteroid in combination with tazarotene as compared with patients treated with low-potency corticosteroid in combination with tazarotene, or tazarotene alone. In particular, we note that patients suffered greater burning when treated with a combination of tazarotene and high-potency corticosteroid and a higher incidence of pruritus when treated with a combination of mid-potency corticosteroid and tazarotene." Decision, bridging paragraph, pages 5-6, emphasis added.

3. "Figure 2 shows treatment success in patients over a 12 week treatment period and four week post treatment period using the same four compositions. As with the results shown in Figure 1, it appears that the combination of low-potency corticosteroid and tazarotene provides better results than the combination of mid-potency corticosteroid and tazarotene." Decision, page 6, emphasis added.

4. "We do not find this Example [(Example 2)] persuasive in demonstrating unexpected results since the Example is unsupported by any data and is merely appellant's assertions that higher treatment success rates and decreased incidence of adverse events were provided when tazarotene was utilized in combination with mid- or high-potency corticosteroids." Decision, bridging paragraph, pages 6-7, emphasis added.

In response to the Decision, appellant elected to amend the claims and continue prosecution before the examiner. Specifically, appellant removed all references to "mid-potency corticosteroid" in the claims. Accordingly, the only corticosteroid encompassed by the claims before us on appeal is a "high-potency corticosteroid."

Against this backdrop, we now consider the merits of the rejection before us on appeal.

## DISCUSSION

According to the examiner (Answer, page 3), the basis for the "rejection is set forth in a Board Decision mailed on September 24, 2003." We emphasize, however, that the scope of the claimed invention now before us on appeal is

different than the scope of the claimed invention in the previous appeal. Accordingly, the prior Merits Panel's findings of fact Nos. 1 and 3, discussed above, are no longer relevant to the claims now on appeal. Specifically, these findings address appellant's evidence, presented in Example 1, Figure 1 and Figure 2, regarding a combination of tazarotene and a low-potency corticosteroid relative to the combination of tazarotene and a mid-potency corticosteroid. The claims now on appeal are limited to a high-potency corticosteroid. As the appellant's evidence demonstrates in Example 1, Figure 1 and Figure 2, a combination of tazarotene and a high potency corticosteroid was more efficacious than the other combinations tested. See also Brief, page 3.

Appellant does not argue the merits of the combination of Yamamoto with Nagpal. Instead, appellant asserts (Brief, page 3), "[a]pplicant believes the specification of the present application contains evidence of unexpected results which are sufficient to overcome the obviousness rejection for the scope of the claims as currently amended, notwithstanding any prima facie [sic] obviousness that [e]xaminer and the Board allege exists." We interpret this statement to mean that appellant has conceded that the examiner has met her burden of establishing a prima facie case of obviousness. Accordingly, we turn to appellant's evidence of unexpected results.

In this regard, appellant points out (Brief, bridging sentence, pages 3-4), "[a]ccording to the Board's observations [in Appeal No. 2002-1369], increasing the potency of the corticosteroid has no apparent advantage in combinations up to mid-potency corticosteroids, thus it is surprising that the combination of

tazarotene and a high-potency corticosteroid should have such a significant improvement over the other treatments." More specifically, appellant asserts (Brief, page 4), Figure 1

> shows a clinically significant reduction in plaque elevation for the tazarotene/high-potency corticosteroid combination compared to the other treatments. Thus, the combination of tazarotene and a high-potency corticosteroid represents a subset which has enhanced efficacy relative to the larger group represented by the combination of tazarotene and a corticosteroid, which enhanced efficacy would not be predicted based upon the properties of the remaining part of the larger group.

Stated differently, the evidence of record demonstrates an unexpected result for the combination of tazarotene and a high-potency corticosteroid. We agree.

The examiner, however, is unconvinced. As we understand the examiner's assertion (Answer, page 5), the evidence of record does not provide a "true side-by-side comparison" of the reagents because different concentrations of corticosteroids were used. More specifically, in the Final Office Action[6], the examiner points out (bridging paragraph, pages 2-3), "Example 1 and the Figures compare alternative topical application of 0.1% tazarotene gel and a placebo, 1% hydrocortisone acetate (low-potency corticosteroid), 0.05% alcometasone dipropionate (medium-potency corticosteroid) or 0.1% betamethasone valerate (high-potency corticosteroid)." According to the examiner (Final Office Action, page 3), "in order to argue unexpected and/or unobvious results, the amount of corticosteroid in each case has to be kept constant."

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[6] Mailed December 3, 2003.

However, as appellant points out (Brief, page 5), since the potencies of the corticosteroids differ, a "comparison of a concentration of one compound to a concentration of a different compound is not proper." Rather, as we understand appellant's argument (Brief, page 6), the use of different concentrations of each corticosteroid effectively "normalizes" the cortocosteroids relative to their potency. According to appellant (id.),

> The potency of the corticosteroid is assigned according to the particular formulation in which it is contained. Thus, the 1% hydrocortisone acetate formulation used in the patent specification is considered to be low-potency at a concentration of 1% in the vehicle it is administered. The same is true for 0.05% alcometasone dipropionate being a medium-potency corticosteroid and 0.1% betamethasone valerate being a high-potency corticosteroid.

According to appellant (id.), "[t]he whole point of assigning potency to a corticosteroid formulation is to indicate the activity of that formulation, and thus treatment for a particular condition is determined according to the assigned potencies of the various corticosteroid formulations." In support of this assertion appellant relies on Cornell[7]. The examiner, however, fails to address appellant's argument or the Cornell reference, maintaining instead (Answer, page 5),

> [t]he examiner sees no reason why applicant could not utilize similar amounts of corticosteroids in each case. In addition, the utilization of low-, mid- and high-potency would imply that at identical concentrations, the efficacy of corticosteroids would be as recited and, thus, the skilled artisan would expect the high-potency corticosteroid to be most effective when used at similar concentration as the others.

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[7] Cornell et al. (Cornell), "Correlation of the Vasoconstriction Assay and Clinical Activity in Psoriasis," Arch Dermatol, Vol. 121, pp. 63-67 (1985).

The examiner, however, appears to miss the point. As the examiner recognizes the concentration of high-potency corticosteroid used in the experiments was 10-fold less than the concentration of low-potency corticosteroid. As appellant points out (Brief, page 6), the

> [e]xaminer's position is inconsistent with itself in that [e]xaminer alleges "[t]he skilled artisan would have the reasonable expectation that the higher concentration of betamethasone valerate [(a high-potency corticosteroid)] would result in better improvement over treatment with lower concentrations of alcometasone dipropionate [a medium-potency corticosteroid)]" but fails to recognize that the same reasoning would lead a skilled artisan to expect that the lower concentrations of alcometasone dipropionate [(a medium-potency corticosteroid)] and betamethasone valerate [(a high-potency corticosteroid)] relative to hydrocortisone acetate [(a low-potency corticosteroid)] would result in the treatment by the former two compounds being less effective. If the former two treatments are expected to be less effective, then the significant improvement of betamethasone valerate [(a high-potency corticosteroid)] over hydrocortisone acetate [(a low-potency corticosteroid)] that was observed must be unexpected.

Accordingly, we are not persuaded by the examiner's unsupported assertion regarding appellant's evidence.

Further, regarding the evidence presented in Table II of the specification, page 12, appellant asserts (Brief, page 4), "[a]ccording to Table II, the adverse events associated with the tazarotene/high-potency corticosteroid combination is at least as low or lower, than the other combinations with the exception of burning. Furthermore, the trend in the total number of adverse events points to a significant advantage for the tazarotene/high-potency corticosteroid combination." In support of this assertion, appellant provides the following table

(id.), which illustrates the downward trend in the total number of adverse events with increasing potency of the corticosteroid.

| | Patients (%) | | | |
|---|---|---|---|---|
| | Taz/plac | Taz/low | Taz/med | Taz/high |
| Total Adverse Events | 41 | 39 | 31 | 26 |

In view of the data tabulated in appellants table of "Total Adverse Events", we agree that the total number of adverse events is lower with the combination of Tazarotene with a high-potency corticosteroid that with tazarotene alone or with a low-potency corticosteroid.

As set forth in In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986):

> If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed. In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984).

On reflection, having considered appellant's evidence and rebuttal arguments in the context of the claims now before us on appeal, we find that the evidence of record weighs in favor of non-obviousness. Accordingly, we reverse the rejection of claims 3, 5-8 and 10-13 under 35 U.S.C. § 103 as being unpatentable over Yamamoto and Nagpal.

## OTHER ISSUES

We note that claim 11 appears to contain a typographical error with reference to the claim from which it depends. As it now reads, claim 11 depends from itself. Prior to any further action on the merits, we encourage the examiner and appellant to work together to resolve this issue.

## REVERSED

William F. Smith
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Linda R. Poteate
Administrative Patent Judge

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